	L #	Hits	Search Text
1	L1	375625	stabilizing or buffer or isotonic or surfactant
2	L2	323	deamidation
3	L3	271	1 and 2
4	L4	42764	sorbitol
5	L5	55	3 and 4
6	L6	503	514/970.ccls.
7	L7	2833	(leukemia adj inhibitory adj factor) or lif
8	L8	1	6 and 7
9	L9	44535	polysorbate or polyoxyethylene or polyoxyethylene-polyoxypropylene
10	L10	44	3 and 9

	L #	Hits	Search Text
1	L1	2833	(leukemia adj inhibitory adj factor) or lif
2	L2	375625	stabilizing or buffer or isotonic or surfactant
3	L3	59251	stabilizer
4	L4	915	1 and (2 or 3)
5	L5	340151	citrate or phosphate or acetate
6	L6	679	4 and 5
7	L7	42764	sorbitol
8	L8	92	4 and 7
9	L9	44535	polysorbate or polyoxyethylene or polyoxyethylene-polyoxypropylene
10	L10	62	4 and 9
11	L11	16569	(fatty adj alcohol) or (glyceryl adj ester) or (fatty adj ester)
12	L12	62	4 and 10
13	L13	323	deamidation
14	L14	13	6 and 13
15	L15	129	8 or 10 or 12 or 14
16	L16	323	deamidation
17	L17	13	15 and 16

BSPR:
When developing a liquid formulation, many factors are taken into consideration. Short-term, i.e., less than six months, liquid stability generally depends on avoiding gross structural changes, such as denaturation and aggregation. These processes are described in the literature for a number of proteins, and many examples of stabilizing agents exist ("Strategies to Suppress Aggregation of Recombinant Keratinocyte Growth Factor during Liquid Formulation Development", B. L. Chen et al., J. Pharm. Sci. 83(12):1657-1661, (1994); "Formulation Design of Acidic Fibroblast Growth Factor", P. K. Tsai et al., Pharm. Res. 10(5):649-659 (1993); "The Stabilization of Beta-Lactoglobulin by Glycine and NCl", Tsutomu Arakawa, Biopolymers 28:1397-1401 (1989); "Structural stability of lipase from wheat germ", A. N. Rajeshwara and V. Prakash, Internat. J. of Peptide & Prot. Res. 44:435-440 (1994); "Thermal Stability of Human Immunoglobulins with Sorbitol ", M. Gonzalez et al., Vox Sang 68:1-4 (1995)). It is well known that an agent effective at stabilizing one protein actually acts to destabilize another. Once the protein has been stabilized against gross structural changes, developing a liquid formulation for long-term stability (greater than six months, for example) depends on further stabilizing the protein from types of degradation specific to that protein. More specific types of degradation may include, for example, disulfide bond scrambling, oxidation of oligosaccharides and/or certain residues, deamidation, cyclization, and the like. Although it is not always possible to pinpoint the individual degradation species, assays are developed to monitor subtle changes so as to monitor the ability of specific excipients to uniquely stabilize the protein of interest.

European Patent Application Publication No. 0 211 601 discloses the
stabilization of growth promoting hormones in a gel matrix formed by a block
copolymer containing polyoxyethylene-polyoxypropylene units and having an
average molecular weight of about 1,100 to about 40,000.